Glucose Homeostasis

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By the end of this lecture the student will be able to:

1. **Outline sources of blood glucose.**
2. **Outline hormonal regulation of metabolic pathways**
3. **Categorize the metabolic effects and regulators of Insulin and glucagon Release**
4. **Interpret different regulatory mechanisms of the main metabolic pathways in different organs in the fed- fast state**

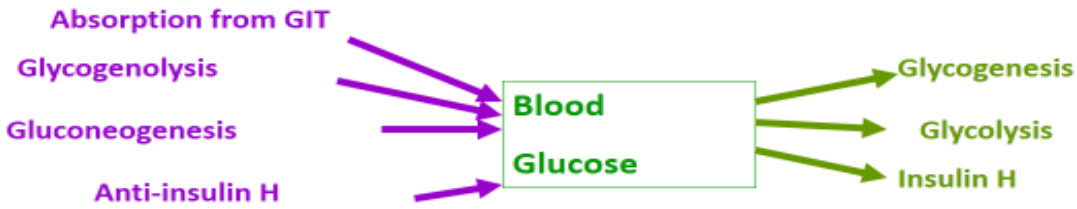
Blood Glucose

Normal Fasting blood glucose = 70-110 mg%

Normoglycemia : blood glucose within normal range

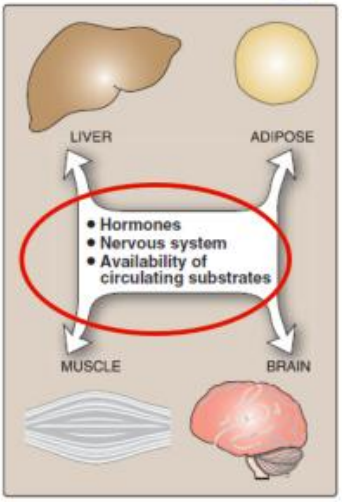
Hyperglycemia : blood glucose above normal range

Hypoglycemia : blood glucose below normal range



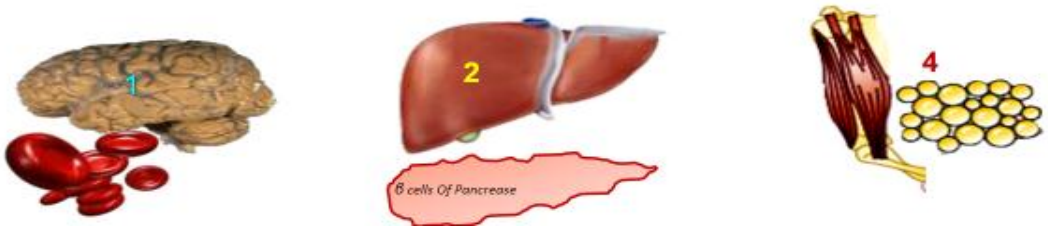
Four major organs play a dominant role in fuel metabolism

- Each organ is specialized for storage, use, or generation of specific fuels.
- Tissues don't function in isolation, but rather form part of a network that require communication through…



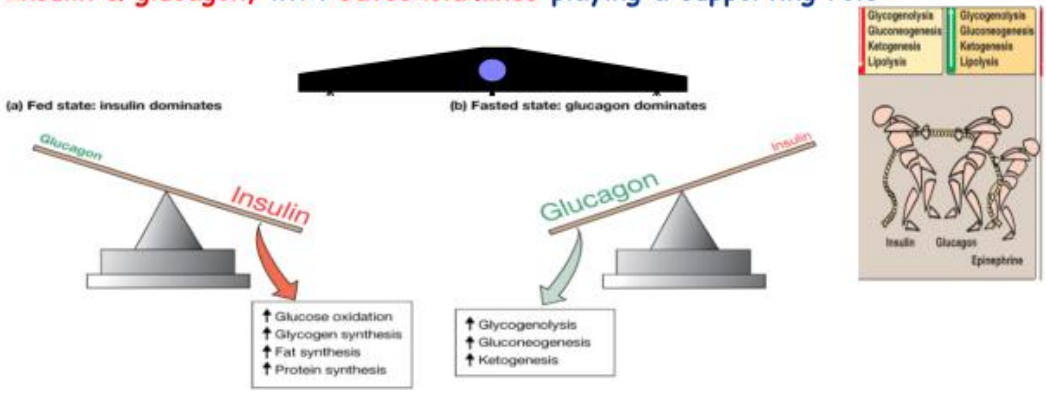
Glucose Transporters

- $GLUT_1$: Brain and RBCs (Insulin-independent).
- $GLUT_2$: Hepatocytes , β-cells of pancreas, intestine (Insulin-independent).
- $GLUT_3$: Brain (Insulin-independent).
- $GLUT_4$: Adipose tissue, Heart and Muscles (insulin dependent)
- $GLUT_5$:Intestinal epithelium (Insulin-independent).



Endocrine Regulation Of Metabolism

Integration of metabolism is controlled 1ry by hormones as:
Insulin & glucagon, with Catecholamines playing a supporting role

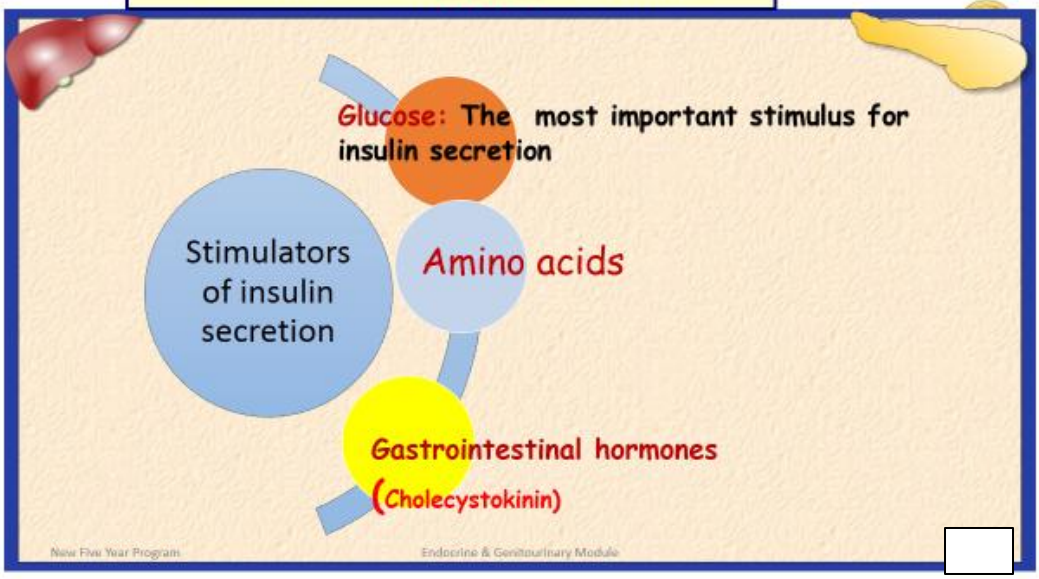


Anti-insulin hormones

1. α-Cells of pancreas : Glucagon
2. Adrenal medulla : Epinephrine.
3. Adrenal cortex : corticosteroides
4. Anterior pituitary homones:
   * ACTH
   * TSH
   * Growth hormone.

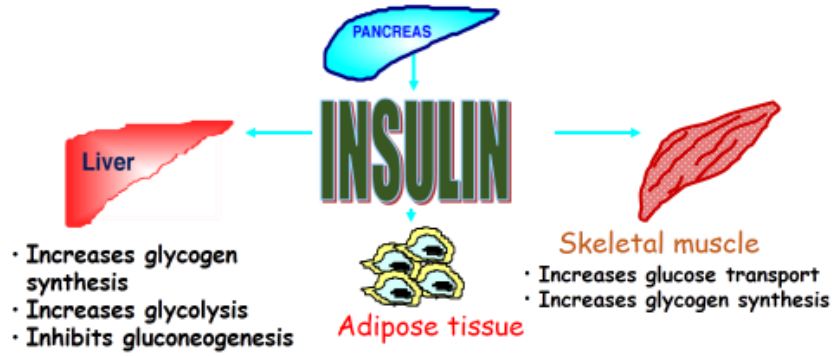
All theses hormones released in response to hypoglycemia

Stimulation of insulin secretion



Metabolic effect of insulin

Has hypoglycemic effect



- Increases glycogen synthesis
- Increases glycolysis
- Inhibits gluconeogenesis

- Increases glucose transport
- Increases glycogen synthesis

- Increases glucose transport
- Increases lipogenesis
- Inhibits lipolysis

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Regulation of glucagon secretion

Stimulation

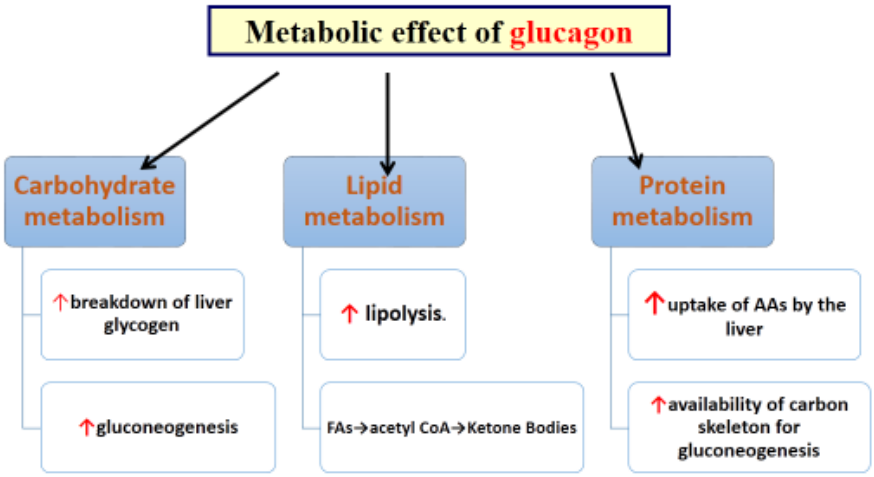
1) Low blood glucose

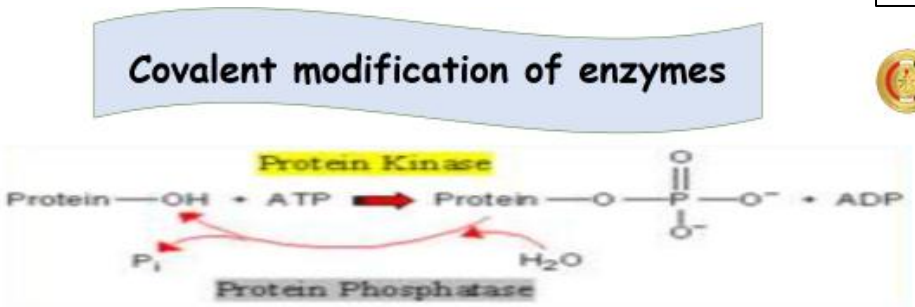
2) Dietary Amino Acids.

3) Elevated levels of circulating epinephrine and norepinephrine in stress, trauma or severe exercise

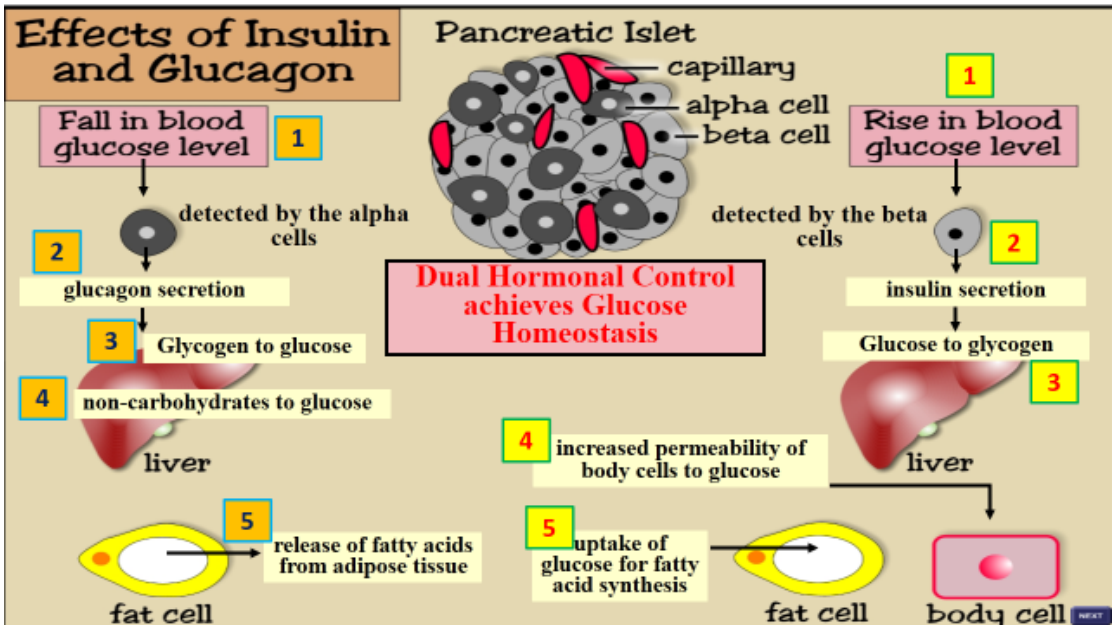
Inhibition

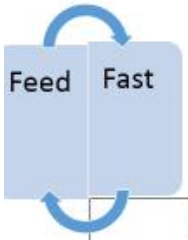
Elevated blood glucose and by insulin





- Many enzymes are regulated by addition or removal of phosphate groups to enzyme
- In fed state, insulin activate enzymes in the dephosyrelated form.
- In fast state, glucagon activate enzymes in the phosyrelated form.





Post Absorptive state
Overnight fast after a meal

Fast lasting 12-24 Hours

Fast lasting > 3days

Prolonged Starvation

Post absorptive state after a meal	**Early fasting state during the night** (> 4 hrs from last meal).
Prolonged starvation	**Refed state**

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Overview of the Post Absorptive State

The post absorptive (well fed) state

- 2 to 4 hrs after ingestion of a normal meal
- Transient ↑ in plasma glucose, AAs, & TAG.
- ↑ I/G ratio
- Anabolic period (TAG glycogen to replenish fuel stores)
- all tissues fuel, Use glucose as a fuel in liver, adipose tissue, muscle, and brain.
- protein synthesis

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Fasting state

(> 4 hrs from last meal)

↓ Plasma levels of glucose, AAs, TAG

- ↓ I/G ratio with Increase release of epinephrine
- Catabolic period (degradation of TAG, glycogen, & protein)
- Need to maintain adequate plasma levels of Glu to sustain energy to brain, RBCs & other Glu requiring tissues
- glucose Production from liver by gluconeogenesis
- FAs Mobilization from adipose tissue
- Synthesis & release of KBs from liver

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The metabolic changes observed in fasting are generally opposite to those described for the well-fed state

Fed state	Fasting
· Most of the enzymes regulated by covalent modification are dephosphorylated and active	· Enzymes are phosphorylated and active. · *glycogen phosphorylase* · *glycogen phosphorylase kinase* · *Hormone-sensitive lipase*

I-Role of liver

major site of regulation of blood glucose

A. Carbohydrate metabolism

Well fed

1. Liver utilize glucose to produce energy via glycolysis
2. It store the excess glucose in the form of glycogen by glycogenesis.

Fasting

The liver first uses **glycogen degradation**

FOLLOWED BY

The liver uses **gluconeogenesis** to maintain blood glucose levels.

1- Increased glycogenolysis:

- ↓ I/G causes rapid mobilization of liver glycogen
- glycogen is nearly exhausted after 10-18 hrs of fasting
- Transient response to early fasting

Increased gluconeogenesis:

- Begins nearly 6 hrs after last meal
- fully active after complete depletion of liver glycogen
- Gluconeogenic precursors (lactate, glycerol & AAs). Energy obtained from fatty acid oxidation from lipolysis
- Important in short & prolonged fasting
- Liver removes amino acids from circulation (proteolysis)

Please Notice This

Liver glycogen degradation: Liver contains glucose 6- phosphatase which hydrolyzes glucose 6 - phosphate to glucose and Pi (This enzyme is not present in muscles, so liver glycogen replenishes blood glucose not muscles glycogen)

Please Notice This

Presence of glucose-6-phosphatase in liver allows release of free Glu to blood both from glycogenolysis and gluconeogenesis

B. Fat metabolism

Increased FAs Oxidation

- ↑ of lipolysis i.e. mobilization of FAs from adipose tissue to liver
- Subsequent drop in level of malonyl COA due to inactivation of ACC by Ⓟ
- This removes inhibitory effect on CPT-1 allowing B-oxidation to proceed
- FA oxidation provides NADH & ATP required for gluconeogenesis & acetyl COA (stimulator for PC & substrate for KBs

Please Notice This

FA oxidation is the major source of energy in hepatic tissue in the postabsorptive state

Acetyl COA can't be used as a substrate for gluconeogenesis?

PDH reaction is irreversible

↑Synthesis of KBs

B. Fat metabolism

Starts during the first days(*3ed day)* of starvation

Favored when conc. of acetyl-COA produced > oxidative `capacity of TCA

Sources of acetyl COA: Oxidation of FAs

The liver is unique in being able to synthesize & release KBs for use by peripheral tissues

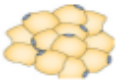
The liver can't use KBs as a fuel lacks thiopherase

Once the level of ketone bodies in the blood is sufficiently high, it ***will inhibit gluconeogenesis especially from proteins (inhibit muscle proteolysis).***

Please Notice This

Although protein is an energy source, it is a structural & functional component of body
Only 1/3 of the body's protein can be used for energy production without fatally compromising vital functions

II-Adipose Tissue



- Well fed:
- Increase Glucose transportion by Glu4 increase (insulin dependent)
- Results in increase **FA synthesis, that stored as TAG** (increase lipogenesis)

- During fasting:

Low insulin level, so glucose uptake by ADIPOSE TISSUE is decreased

- Results in decrease in **FA** and **TAG** synthesis

Increased degradation of TAG = + of lipolysis

Activation of HSL & subsequent hydrolysis of stored TAG are enhanced by elevated catecholamines

FFAs released are utilized by tissues as a source of energy
Proionyl CoA from oxidation of odd number FA is gluconeogenic precursor by liver

Glycerol is used as a gluconeogenic precursor by liver (glycerol kinase)

III-Skeletal muscles

- Well fed:
- Increase Glucose transportion by Glu4 increase (insulin dependent)
- It store glucose as glycogen.

A.Carbohydrates metabolism

- During fasting
- Low insulin level, so glucose uptake by muscle is decrease

2-Concerning lipid metabolism:

B. Fat metabolism

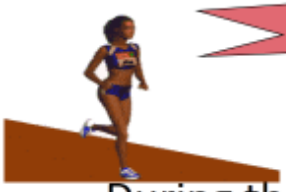
During first 2 weeks of fasting

Ms use FAs from adipose tissue & KBs from liver as fuels

After 3 weeks

Oxidizes FAs almost exclusively→ thus sparing KBs for brain

C. Protein metabolism



During the first few days of fasting

- There is a rapid breakdown of muscle protein
- provides amino acids that are used by the liver for gluconeogenesis.

In prolonged starvation, comatose malnourished patients: Respiratory muscles are the most affected with decrease production of antibodies leading to pneumonia and death

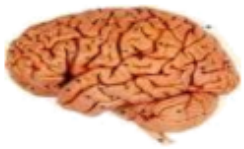
C. Protein metabolism

After about three weeks of fasting

- The rate of muscle proteolysis decreases because there is a decline in the need for glucose as a fuel for the brain, which has begun using ketone bodies as a source of energy.

Alanine and glutamine are quantitatively the most important gluconeogenic amino acids released from muscle.

IV-Brain

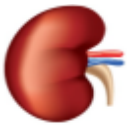


- Well fed: is a major consumer of glucose
- During fasting

1. During the first few days of fasting: The brain continues to use glucose
2. In prolonged fasting

- Plasma ketone bodies reach significantly elevated levels
- So the brain replaces glucose as the primary fuel with ketone bodies.
- This reduces the need for protein catabolism for gluconeogenesis.

5.Role of the kidney



- Glucose is continuously filtered by the glomeruli.
- It is reabsorbed by the renal tubules by an ATP-dependant mechanism.
- The capacity of the tubular system to reabsorb glucose is limited to a blood glucose level of 180 mg %.
- When blood glucose levels are elevated, the capacity of tubular system for glucose reabsorption is exceeded and glucose passes in urine producing glucosuria.
- Glucosuria occurs at glucose concentration exceeding 180 mg %.
- This is termed "the renal threshold for glucose*.

Kidney in Long-Term Fasting

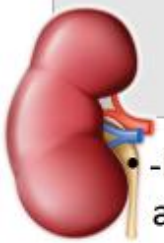
1. **Kidney expresses the enzymes of gluconeogenesis.**

2-The **glutamine** released from the muscle's metabolism is taken up by the kidney

Glutamine acted upon by ***renal glutaminase*** and ***glutamate dehydrogenase***, producing **α-ketoglutarate**, plus **ammonia.**

Kidney in Long-Term Fasting

The **ammonia** picks up **H+** from ketone body dissociation, and is excreted in the urine as **NH4+ ammonium ion**, decreasing the acid load in the body.



-Kidney also provides compensation for the **acidosis** that accompanies the **increased production of ketone bodies**. Via excess excretion of **NH4**

======== ***Thank You ======***

=========Marwa Dahpy=======